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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,956	10/23/2001	Melissa K. Carpenter	091/009C	1602

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,956	CARPENTER ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11-17,30-32,35 and 37-52* is/are pending in the application.

4a) Of the above claim(s) *1,11-15,17,30-32 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *16 and 37-52* is/are rejected.

7)☒ Claim(s) *16, 40-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12/13/01* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's Amendment, filed 1/9/04, has been entered. Claims 1, 11-17, 30-32, 35, 37-52 are pending. Claims 16 and 17-52 are under current examination.

Election/Restrictions

Applicant's election without traverse of claim 16 (Group VI) in the paper filed October 23, 2003, is acknowledged. Newly added claims 17-52 are found to fall within Group VI, and thus, will be examined along with claim 16. Claims 1, 11-15, 17, 30-32 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in the paper filed on October 23, 2003.

Priority

This Application claims priority to 09/688,031, filed October 10, 2000 [see p. 2, 2nd ¶], which does not appear in Applicant's Oath/Declaration. It is unclear what priority Applicants are claiming (i.e., a continuation, a continuation-in-part, etc.). Clarification is required.

This Application further claims benefit to PCT/US01/01030, filed January 10, 2001. See p. 2, 2nd ¶. This application does not appear in Applicant's Oath/Declaration under 35 U.S.C. §119 and no certified papers have been received.

Thus, it is unclear what priority Applicants are claiming (i.e., a continuation, a continuation-in-part, etc.). Clarification is required.

Claim Objections

Claim 16 is objected to for the following reason: The claim is dependent upon a non-elected claim [claim 15]. Applicant is required to rewrite the claim in independent form.

Claim 40 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recites that the cells have been caused or permitted to differentiate before being contacted with the substance. The independent claim recites a method for screening a substance by contacting a differentiated cell with the substance. Thus, the cells would be differentiated in order to carry out the method of contacting and therefore the claim does not further limit the parent claim. Claims 41-44 are dependent upon claim 40.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214

USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 16, 37, 40, 42, 45-50 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 34 and 47 of copending Application No. 09/888,309. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass the methods for testing a substance on differentiated cells. The instant claims are directed to methods for screening a substance, comprising contacting a differentiated cell with a substance and determining any phenotypic or metabolic changes in the cell that result from the contact. In further embodiments, the differentiated cell is produced by differentiating a culture of pPS cells. The '309 claims are directed to methods for testing a substance for its effect on differentiated cells, wherein the cells are produced by differentiating human ES cells, and determining any phenotypic or metabolic changes in the cell population that result from contact with the substance, and correlating the change with cellular toxicity or modulation caused by the substance. Accordingly, the instant claims are rendered obvious over the '309 because both encompass to the same methods of screening differentiated cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16, 37, 40, 42, 43 and 45 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 11 of copending Application No. 10/157,288. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass the methods for testing a substance on differentiated cells. The instant claims are directed to methods for screening a substance, comprising contacting a differentiated cell with a substance and determining any phenotypic or metabolic changes in the cell that result from the contact. The '288 claims are directed to methods of screening a compound for its effect on neural cells or a neural cell activity, by obtaining an established line of pPS cells wherein at least 60% of the cells express A2B5, NCAM, MAP-2 or Nest, combining the cells with the compound, determining any change to phenotype or activity of the cells that results from being combined with the compound and correlating the change with an effect on the compound on neural cells or a neural cell activity. Thus, the instant claims, which recite, "differentiated cells" encompass the cells [cells expressing neuronal markers] claimed in the '288 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16, 37, 40, 42, 45-50 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 21 of copending Application No. 10/087,473. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass the methods for testing a substance on differentiated cells. The instant claims are directed to methods for screening a substance, comprising contacting a differentiated cell with a substance and determining any phenotypic or metabolic changes in the cell that result from the contact. The '473 claims are directed to methods of screening for cellular toxicity or modulation by combining a compound with a committed or differentiated cell prepared by differentiating pPS cells, and determining any phenotypic or metabolic changes in the cell that result from contact with the compound, and correlating the change with cellular toxicity or modulation. Accordingly, the instant claims are made obvious by the '473 claims because the instant claims recite methods of screening, and claim particular phenotypic or metabolic changes such as differentiation [claim 47], growth [claim 46], for example.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16, 37, 40, 42, 44-50 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 14 and 15 of copending Application No. 10/087,142. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass the methods for testing a substance on differentiated cells. The instant claims are directed to methods for screening a substance, comprising contacting a differentiated cell with a substance and determining any phenotypic or metabolic changes in the cell that result from the contact. The '142 claims are directed to screening compounds for hepatocellular toxicity and methods for screening compounds which modulate hepatocellular function by combining a cell differentiated from pPS cells with a compound, and determining any phenotypic or metabolic change in the cell. The instant claims are rendered obvious in view of the '142 claims because the instant claims recite, "differentiated" cells, which are encompassed by the hepatocytes of the '142 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16, 37, 40, 42, 45-50 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 17 of copending Application No. 10/313,739. Although the conflicting claims are not identical, they are not patentably distinct

from each other because both sets of claims encompass the methods for testing a substance on differentiated cells. The instant claims are directed to methods for screening a substance, comprising contacting a differentiated cell with a substance and determining any phenotypic or metabolic changes in the cell that result from the contact. The '739 claims are directed to methods of screening a compound for its ability to modulate islet cell function by combining the compound with a differentiated cell population, produced by differentiating pPS cells, and determining any phenotypic or metabolic changes in the cell population. The instant claims are rendered obvious by the '739 claims because the instant claims are directed to, "differentiated cells" which are encompassed by the islet cells of the '739 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 16, 37, 40, 42, 45-50 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11-13 of copending Application No. 10/189,276. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass the methods for testing a substance on differentiated cells. The instant claims are directed to methods for screening a substance, comprising contacting a differentiated cell with a substance

and determining any phenotypic or metabolic changes in the cell that result from the contact. The '276 claims are directed to methods of screening a compound for mesenchymal cell toxicity or modulation, by combining the compound with a population of mesenchymal cells produced by differentiation of pPS cells, and determining any mesenchymal cell toxicity or modulation resulting from the compound. The instant claims are rendered obvious by the '276 claims because the instant claims are directed to, "differentiated cells" which are encompassed by the mesenchymal cells of the '276 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16 and 17-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of screening a substance, comprising a) obtaining a culture of undifferentiated pPS cells proliferating on an extracellular matrix and in the presence of fibroblast-conditioned medium, wherein the culture is essentially free of feeder cells, b) causing or permitting the pPS cells to differentiate; then c) combining the cells with

the substance; and d) determining the phenotypic or metabolic effect of the substance on the cells; does not reasonably provide enablement for the methods of screening a substance comprising contacting a differentiated cell with a substance and determining any phenotypic or metabolic changes that result in the cell from contact with the compound, wherein the differentiated cell is produced by obtaining a culture of undifferentiated pPS cells proliferating in a growth environment that is essentially free of feeder cells and optionally causing or permitting the pPS cells to differentiate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to screening a substance by contacting a differentiated cell with the substance and determining any phenotypic or metabolic changes in the cell that result from contact with the substance. In further embodiments, the differentiated cell is produced by permitting primate pluripotent stem [pPS] cells to differentiate.

The specification teaches that the undifferentiated pPS cells of the instant invention would be cultured in the absence of feeder cells, and that the role of feeder cells is replaced by culturing the pPS cells on an extracellular matrix with a cultured medium. See p. 3, lines 29-31. The specification teaches that cells used to condition the medium include primary embryonic fibroblasts, telomerized fibroblasts, and fibroblast-like cells differentiated and selected from cultured pPS

cells. See p. 6, lines 38-41. The specification teaches that non-human cells, which have the morphology of fibroblasts and of early muscle and neuronal cells may be used to produce conditioned media. Further, certain fibroblast-like cells (or mesenchymal cells) derived from human embryo cells can be used to condition the media. See p. 17. The specification teaches that the pPS cells can be proliferated without promoting differentiation when they are cultured on an extracellular matrix component, such as Matrigel®, laminin, fibronectin, etc., and that a conditioned medium supplies the elements that are normally provided by feeder cells. See pp. 15-16. The specification teaches the culture of undifferentiated human ES cells in feeder free conditions, wherein the cells were cultured on Matrigel® in a conditioned medium from primary mouse embryonic fibroblasts [mEF]. See Example 1. The specification further teaches that human ES cells were cultured on Matrigel or gelatin in mEF conditioned medium. It was found that the cells that were cultured on Matrigel remained undifferentiated, whereas the cells cultured on gelatin appeared differentiated. See Example 2. The specification teaches alternative cell lines were tested for their ability to support the growth of hES cells in feeder free culture. Primary mouse embryonic fibroblasts [mEF], a telomerized mEF cell line [NHG190], a transformed mouse fibroblast cell line [STO], a telomerized human foreskin fibroblast cell line [BJ 5ta] and a telomerized human retinal epithelial cell line [hTERT-RPE] were used to condition medium. The pPS cells were then cultured in the conditioned mediums. It was

found that all conditioned medium supported undifferentiated pPS cells, except the hTERT-RPE cell line, wherein the cells differentiated within the first week of culture. See Example 11 and Figure 1, Panel B. pPS cells were also cultured in medium which was conditioned by human embryonic fibroblast-like cells from the H9 stem cell line. See Example 12.

The claims, as broadly written, fail to enable the claimed invention because they encompass culturing the pPS cells in feeder free conditions in any growth environment. The state of the art of culturing of primate embryonic stem cells is such that culturing typically requires the presence of feeder cells. Thomson *et al.* discuss the difficulties in culturing pPS in feeder free conditions. Thomson *et al.* (PNAS, 92:7844-7848, 1995, Reference CN of Applicants' IDS, field 12/13/01) teach the derivation of a cloned cell line from a rhesus monkey that remains undifferentiated when grown on mouse embryonic fibroblast feeder layers, but differentiate or die in the absence of the fibroblasts (see p. 7844, *Abstract*). Particularly, Thomson *et al.* state that in the absence of the feeder layers, soluble human leukemia inhibitory factor (LIF) fails to prevent the differentiation of the cells, and that the factors that fibroblasts produce to prevent the differentiation of the cells is yet unknown (see p. 7847, 1st column, 2nd paragraph). Thomson *et al.* further state that human inner cell mass-derived cells were cultured in the absence of feeder layers failed to survive beyond 2 passages (see p. 7848, 1st paragraph). The instant specification supports Thomson's finding, stating that, "[T]he role of the

feeder cells is replaced by supporting the culture (of pPS cells) on an extracellular matrix and culturing the cells in a conditioned medium." See p. 3, lines 29-31. The specification fails to provide or teach any other conditions in which pPS cells could be grown in feeder-free conditions in the absence of an extracellular matrix and as such, the claimed invention is enabling only for culturing the described pPS cells in the presence of an extracellular matrix.

Furthermore, the claims as broadly written do not specify a type of medium in which the hES cells would be cultured. The state of the art of culturing ES cells is unpredictable. Lim *et al.* [**Proteomics**, 2:1187-1203(2002)] teach the proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers to characterize the environment that supports the growth of undifferentiated human ES cells, and to identify factors critical for their independent growth. See *Abstract.* Lim state that, "Despite many years of using mouse embryonic fibroblast cells as feeder support of human ES cells, it is still not clear what these cells for their clients. The interaction between these two cell types might take place *via* factors secreted into the medium or into extracellular matrix as well as through membrane-bound proteins." See p. 1188, 1st ¶. Lim teach that by utilizing proteomic analysis, unexpected results identify many known intracellular proteins, and that further analysis using serum-containing medium in the presence of ES cells, and using other cell types for feeder layers will be required. See p. 1203, 1st ¶, #4. As specific factors that support undifferentiated growth of hES cells have yet to be identified, it

would not be predictable that any media, when used as claimed, would maintain hES cells in an undifferentiated state. The specification provides support for fibroblast-conditioned medium [see Examples 11-12] and further shows that a non-fibroblast conditioned medium, hTERT-RPE, fails to support undifferentiated growth of the pPS cells. Accordingly, in light of the teachings and the specification, pPS cells cultured on an extracellular matrix with fibroblast-conditioned medium would be expected to maintain the cells in an undifferentiated state, as required by the claims.

Accordingly, in view of the unpredictable nature of culturing undifferentiated pPS cells in any particular feeder-free condition, the lack of direction or guidance provided by the specification for culturing the undifferentiated pPS cells under any feeder-free condition, other than the exemplified condition, wherein the undifferentiated pPS cells have been maintained in a culture environment comprising an extracellular matrix component with fibroblast-conditioned media, as well as the unpredictable state of the art of any particular media which would be used to culture the pPS cells in an undifferentiated state and the lack of working examples to show that any media, other than the exemplified fibroblast-conditioned medias, would be sufficient to maintain the pPS cells in an undifferentiated state it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37, as written, is confusing. The claim recites that the undifferentiated pPS cells are "optionally" caused to differentiate in part (b) of the claim. This is unclear because the method is directed to screening a substance by contacting a differentiated cell with the compound. Thus, the method requires that the cells utilized be differentiated. Claims 38-52 depend from claim 37.

Claim 39, as written, is unclear. The claim recites that the cells are undifferentiated when contacted with the substance, however, the independent claim recites methods for screening a substance by contacting a differentiated cell with a compound. Thus, the cells could not be undifferentiated when contacted with the substance, as claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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